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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/017,643	12/12/2001	Thomas C. Terwilliger	S-96,583	7287

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EXAMINER	
DEJONG, ERIC S	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 06/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/017,643	TERWILLIGER, THOMAS C.	
	Examiner	Art Unit	
	Eric S. DeJong	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7 and 8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 7, and 8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED OFFICE ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10 June 2005 has been entered.

Specification

The previous objection to the disclosure is withdrawn in view of the amendment filed by applicant on 10 June 2005.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 7, and 8 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Murshudov et al. This rejection is reiterated and maintained from the previous Office action, mailed 09 May 2005.

The instant claims are drawn to a method for improving an electron density map representing a crystal structure comprising the steps of obtaining crystallographic amplitudes for a plurality of reflection from a crystal structure, deriving a first electron density map from a first set of structure factors, establishing crystallographic phases for

each reflection by identifying features from the first map, comparing the first electron density map with an expected electron distribution, and estimating changes possible crystallographic phases, then deriving an updated electron density map using the observed structure factor amplitudes and the crystallographic phases determined to be the most probable. The above steps are then reiterated in order to generate a final electron density map using a final set of crystallographic phases.

Claim 1: Murshudov et al. discloses the application of maximum likelihood calculations to improve x-ray structural refinement and determination methodologies and reduce model bias in map calculations (a method for improving an electron density map representing a crystal structure, minimum bias from known electron density maps). See Murshudov et al., page 241, column 2, lines 18-50 and page 242, column 1, lines 24-38. Murshudov et al. provides a basis for the computations of maximum likelihood with an evaluation of the posterior probability distribution, P, which incorporates the experimental data |F|, wherein |F| is defined as experimental amplitude of the structure factors obtained by x-ray crystallography (step (a) obtaining x-ray diffraction observed structure factor amplitudes for a plurality of reflections). See Murshudov et al., at least page 240, column 1, lines 25 and 26 and page 242, column 1, line 46 through column 2, line 8. In calculating the conditional probability distribution, a function that combines structure factor amplitude and phase information, Murshudov et al. acknowledges that experimental phases are usually not known and accommodates the separate component containing phase information for each reflection as a distribution of phases defined as $P(\phi)$ (step (b) selecting a starting set of crystallographic phases to combine

with the observed structure factor amplitudes). Further, solving the expression provided in equation 8 provides an evaluation of crystallographic structure factors and under a reasonably broad interpretation reads on the claimed first set of structure factors. See Murshudov et al., page 243, column 1, line 9 through page 244, column 2, line 12 and equations 8 and 9. Murshudov et al. further provides examples of using the above calculation in building partial models built on experimentally phased maps and using said maps to generate a useful contribution to the calculated structure factor (step (c) deriving a first electron density map from the first set of structure factors; step (d) identifying features of the first electron density map to obtain expected distributions of electron density; step (e) making a comparison between the first electron density map and the expected distributions of electron density). See Murshudov et al., page 243, column 2, lines 1-23, page 248, figure 2, and page 249, column 1, lines 1-15. In examples applications of the disclosed methodology, Murshudov et al. teach the evaluation of differences between calculated phases determined from current and final models at all stages of the refinement process, which reads on the claimed step (f) estimating how changes in the crystallographic phase of a reflection k affect the comparison. See Murshudov et al., page 246, column 1, line 15 through column 2, line 2. Murshudov et al. discloses derivative forms of the log-likelihood which rely on an evaluation of the prior distribution of phases, $P(\phi)$, and is utilized in evaluating the minimization of the maximum likelihood function that is utilized in the above described refinement procedures (step (g) establishing crystallographic phase probability distributions from the comparisons for the possible crystallographic phases of reflection

k). See Murshudov et al., page 251, column2, line 1 through page 252, column 2, line 26. Further, the above described refinement methodology is recursively performed and evaluated on a number of crystallographic reflections and reads on the claimed method steps of repeating steps (c) through (g) as k is indexed through all of the plurality of reflections. See Murshudov et al., page 245, column 1, line 24 through column 2, line 35.

Murshudov et al. further provides examples where several successive rounds of the above refinement procedures was used to improve upon pre-existing modeling attempts and ultimately produced a final set of structure factors, wherein amplitudes and final phase estimates were combined, that are in turn used to produce electron density maps representing a given protein structure (step (j) deriving an updated electron density map; step (k) repeating steps (d) through (j); step (l) forming a final electron density map using the final set of crystallographic phases). See Murshudov et al. page 247, column 1, line 4 through page 248, column 2, line 8, and Tables 1-3, and Figure 2C.

Claim 2: Murshudov et al. teaches that in the structure refinement and modeling procedure, accommodating identified regions of structure and bulk solvent is handled by additions to the structure factor by modifying equation 9, the expression for probability distribution (making probability estimates of whether each point in the map is located in a solvent region or crystal structure region). See Murshudov et al., page 250, column2, lines 1-41.

Claim 3: In defining the coordinates and form factors for each atom using the Miller index of the reflecting plane, Murshudov et al. teaches that the derivatives of the coordinates can be used in a form function that has the same symmetry as the Patterson function, which under a reasonably broad interpretation reads on the claimed identification of features of the electron density map includes estimates at each point in the map is related by non-crystallographic symmetry to electron density at another point in the map. See Murshudov et al., page 253, column 1, line 1 through column 2 line 17 and equations 42-49.

Claims 4 and 5: Murshudov et al. provides examples of the disclosed refinement method applied to the x-ray crystal structure of cytochrome c', which comprises 8 separate α-helicies. The refinement methodology included an initial electron density map determined by a different refinement method and allowed for comparison determinations between intermediate and final electron density map calculations (wherein identifying features of the electron density map includes estimates of whether a structural motif is located at each map point; wherein the structural motif is a helix). See Figure 2 and pages 247, column 1, line 21 through page 249, column 1, line 15.

Claim 6: The refinement methodology disclosed by Murshudov et al. relies upon log-likelihood functions to define and evaluate phase probability distributions (the crystallographic phase probability distributions are log-likelihood functions). See at least Murshudov et al., equations 8-14 and page 243, column 1, line 5 through page 244, column 2, line 12.

Claim 7: Murshudov et al. discloses first and second derivatives of log-likelihood functions pertaining to the determination of the distribution of phases as well as Fast-Fourier Transform operations in determining maximum likelihood through the minimization procedures of said likelihood functions (steps of calculating first and second derivatives; applying a Fast Fourier Transform based algorithm to determine probable crystallographic phase probability distributions). See Murshudov et al., page 253, column 1, line 13 through page 253, column 2, line 26 and equations 24-40.

Claim 8: The disclosed example of cytochrome c' modeling and refinement by Murshudov et al. reads on the claimed selecting a model crystal structure having similarities to the crystal structure being examined. Further, Murshudov et al. teaches that the current methodologies are improvements upon previous refinement strategies well known in the art that utilize structure factor amplitudes that are weighted in order to reduce refinement bias (assigning a low weighting factor to structure factors of the model crystal; combining the weighted structure factors with the observed structure factors for deriving the first electron density map). See Murshudov et al., page 241, column 1, line 24 through column 2, line 17. Further, Murshudov et al. clearly teaches "recent interest in using these equations for refinement of macromolecular structures has been stimulated by their successful application in reducing model bias in map calculations; by the theoretical results... for their application with maximum entropy as a general tool in phase determination; by their successful application of his results in phase improvement" (emphasis added). See Murshudov et al., page 242, column 1, lines 24-38.

Response to Arguments

Applicants arguments, filed 10 June 2005, have been fully considered but they are not deemed to be persuasive.

Regarding Claim 1, Applicants assert that Murshudov et al. does not teach steps d, e, f, and g of Claim 1, which describes the analysis of an electron density map to obtain expectations about the electron density map distributions in the map, comparisons of the current map with expectations, estimating how changed in structure factors will affect this comparison, and establishing phase probability distributions from these comparisons. Applicants further assert that Murshudov et al. does not teach that certain parts of the electron density map are known accurately and other parts are not. Applicants also assert that the features that are identified in the electron density map are normally not the presence of the atoms in the current atomic model of the macromolecule, but rather a different set of features that yield independent information, and it is the use of this independent information is not taught by Murshudov et al.

Applicants assertion that Murshudov et al. does not teach steps d, e, f, and g of Claim 1, is not found convincing as applicants arguments are not directed to the merits on which the rejection is based. As stated above, Murshudov et al. further provides examples of using the above calculation in building partial models built on experimentally phased maps and using said maps to generate a useful contribution to the calculated structure factor (step (c) deriving a first electron density map from the first set of structure factors; step (d) identifying features of the first electron density map to

obtain expected distributions of electron density; step (e) making a comparison between the first electron density map and the expected distributions of electron density). See Murshudov et al., page 243, column 2, lines 1-23, page 248, figure 2, and page 249, column 1, lines 1-15. In examples applications of the disclosed methodology, Murshudov et al. teach the evaluation of differences between calculated phases determined from current and final models at all stages of the refinement process, which reads on the claimed step (f) estimating how changes in the crystallographic phase of a reflection k affect the comparison. See Murshudov et al., page 246, column 1, line 15 through column 2, line 2. Murshudov et al. discloses derivative forms of the log-likelihood which rely on an evaluation of the prior distribution of phases, $P(\phi)$, and is utilized in evaluating the minimization of the maximum likelihood function that is utilized in the above described refinement procedures (step (g) establishing crystallographic phase probability distributions from the comparisons for the possible crystallographic phases of reflection k). See Murshudov et al., page 251, column2, line 1 through page 252, column 2, line 26..

Contrary to applicants assertion that Murshudov et al. does not teach that certain parts of the electron density map are known accurately and other parts are not, as stated above, Murshudov et al. teaches that in the structure refinement and modeling procedure, accommodating identified regions of structure and bulk solvent is handled by additions to the structure factor by modifying equation 9, the expression for probability distribution. See Murshudov et al., page 250, column2, lines 1-41. In defining the coordinates and form factors for each atom using the Miller index of the reflecting plane,

Murshudov et al. teaches that the derivatives of the coordinates can be used in a form function that has the same symmetry as the Patterson function, which under a reasonably broad interpretation reads on the claimed identification of features of the electron density map includes estimates at each point in the map is related by non-crystallographic symmetry to electron density at another point in the map. See Murshudov et al., page 253, column 1, line 1 through column 2 line 17 and equations 42-49.

Further, the instant claims do not contain any limitation restricting the identification features in the electron density map to exclude the presence of the atoms in the current atomic model of the macromolecule. Therefore, Applicants assertion that the features that are identified in the electron density map are normally not the presence of the atoms in the current atomic model of the macromolecule, but rather a different set of features that yield independent information, and it is the use of this independent information is not taught by Murshudov et al. is not found convincing.

Regarding claims 2-5, Applicants assert that Murshudov et al. does teach the existence of each of these features of a map, but does not teach their use in obtaining a probability distribution for electron density. Applicants assertion is not found persuasive.

As cited above, Murshudov et al. teaches that in the structure refinement and modeling procedure, accommodating identified regions of structure and bulk solvent is handled by additions to the structure factor by modifying equation 9, the expression for probability distribution. See Murshudov et al., page 250, column2, lines 1-41. In defining

the coordinates and form factors for each atom using the Miller index of the reflecting plane, Murshudov et al. teaches that the derivatives of the coordinates can be used in a form function that has the same symmetry as the Patterson function, which under a reasonably broad interpretation reads on the claimed identification of features of the electron density map includes estimates at each point in the map is related by non-crystallographic symmetry to electron density at another point in the map. See Murshudov et al., page 253, column 1, line 1 through column 2 line 17 and equations 42-49. Murshudov et al. provides examples of the disclosed refinement method applied to the x-ray crystal structure of cytochrome c', which comprises 8 separate α-helicies. The refinement methodology included an initial electron density map determined by a different refinement method and allowed for comparison determinations between intermediate and final electron density map calculations. See Figure 2 and pages 247, column 1, line 21 through page 249, column 1, line 15.

Regarding claim 7, Applicants assert that Murshudov et al. teaches the use of maximum-likelihood functions and FFT methods for calculation of derivatives for refinement of macromolecular structures, but does not teach their use in estimating phase probabilities. Applicants assertion is not found persuasive.

As stated above, Murshudov et al. discloses first and second derivatives of log-likelihood functions pertaining to the determination of the distribution of phases as well as Fast-Fourier Transform operations in determining maximum likelihood through the

minimization procedures of said likelihood functions. See Murshudov et al., page 253, column 1, line 13 through page 253, column 2, line 26 and equations 24-40.

Regarding Claim 8, Applicants assertion that Murshudov et al. teaches the use of model structure having similarities to the crystal structure being examined and the use of weighting factors to reduce model bias, but does not teach the use of either in the method of Claim 1. Applicants assertion is not found persuasive.

Conclusion

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. DeJong whose telephone number is (571) 272-6099. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, Ph.D. can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is (571) 272-8300.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instrument Examiner, Tina Plunkett, whose telephone number is (571) 272-0549.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

EDJ EDJ

24 June 2005

JOHN S. BRUSCA, PH.D
PRIMARY EXAMINER